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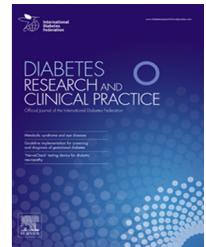
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Body surface area and glucose tolerance – The smaller the person, the greater the 2-hour plasma glucose

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ABSTRACT

Background: The oral glucose tolerance test (OGTT) is standardized globally with a uniform glucose load of 75 g to all adults irrespective of body size. An inverse association between body height and 2-hour postload plasma glucose (2hPG) has been demonstrated. Our aim was to evaluate the relationship between body surface area (BSA) and plasma glucose values during an OGTT.

Methods: An OGTT was performed on 2659 individuals at increased cardiovascular risk aged between 45 and 70 years of age, who had not previously been diagnosed with diabetes or cardiovascular disease. Their BSA was calculated according to the Mosteller formula. Study subjects were divided into five BSA levels corresponding to 12.5, 25, 25, 25, and 12.5% of the total distribution.

Findings: When adjusted for age, sex, waist circumference, alcohol intake, current smoking, and leisure-time physical activity, BSA level showed an inverse linear relationship with the 2hPG in all categories of glucose tolerance (p for linearity < 0.001). Moreover, the smaller the adjusted BSA of the study person, the higher the proportion of newly diagnosed type 2 diabetes based on 2hPG in the OGTT.

Interpretation: Body size has a considerable impact on the findings from a standardized OGTT. Smaller persons are more likely to be diagnosed as glucose intolerant than relatively larger sized individuals.

Funding: This work was supported by the State Provincial Office of Western Finland, the Central Satakunta Health Federation of Municipalities, Satakunta Hospital District, and the Hospital District of Southwest Finland.

Research in context: **Evidence before this study.** We searched PubMed using the MeSH terms “glucose tolerance test”, “body surface area”, “body height”, “body size”, “glucose tolerance”, “insulin resistance”, “blood glucose” and “diabetes mellitus” on March 10, 2019

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without language restrictions. We also used Cited Reference Search in Web of Science for relevant articles. The oral glucose tolerance test (OGTT) is standardized globally with a uniform glucose load of 75 g to all adults irrespective of body size. An inverse association between body height and 2-hour postload plasma glucose (2hPG) has been demonstrated. Several studies have shown that 2hPG predicts all-cause mortality better than elevated fasting glucose. However, body height or body surface area are not usually adjusted in epidemiological studies. It is well known that short adult stature is a risk factor for cardiovascular and all-cause mortality.

Added value of this study. This is the first study to assess the relationship of body surface area and 2hPG in a typical primary care population at increased cardiovascular risk. Body surface area has a considerable impact on the result of a standardized OGTT. Smaller individuals are more likely to be diagnosed as glucose intolerant than relatively larger sized individuals.

Implications of all the available evidence. There is a possibility that the diagnosis of type 2 diabetes made by an OGTT is a false positive result in a relatively small individual, and a false negative result in a relatively larger individual. Association of 2hPG concentrations and mortality may be influenced by body size as confounding factor. Given that the OGTT is a time and effort consuming test both for patients and laboratory personnel, validity of the OGTT for different body sizes should be reconsidered.

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1. Introduction

Fifty years ago, the Committee of the Statistics of the American Diabetes Association proposed an estimation of body surface area (BSA) in order to define the appropriate glucose load to be used during an oral glucose tolerance test (OGTT) [1]. In 1980, the World Health Organization (WHO) recommended the global standardization of OGTT with a uniform glucose load of 75 g [2,3]. This recommendation is still valid [4] although fasting plasma glucose (FPG) and 2-hour postload plasma glucose (2hPG) cut-off levels for glucose disorders are somewhat arbitrary and interpopulation differences in the frequency distribution of plasma glucose (PG) concentrations exist [5]. Observed ethnic differences might be explained by the different means of height of those populations, since several studies have demonstrated an inverse association between body height and 2hPG [6–9]. Moreover, our previous study [10] showed that adult height is inversely related to 2hPG, but only up to a body mass index (BMI) of 35 kg/m².

Given that height is a one-dimensional measure of the human body, we hypothesized that BSA as a total surface area of the human body would be better able to take body size into account when an OGTT is used as a diagnostic method. Moreover, BSA is an absolute measure defined by the area of body surface and as such, maybe a more relevant variable than BMI which is a ratio of weight and the square of height. Fig. 1 shows the interplay between height, BMI and BSA. The effect of height on BSA is more pronounced than that of BMI. The aim of the present study is to evaluate the relationship between BSA and plasma glucose concentrations in an OGTT given to apparently healthy persons, who were at risk for but not previously diagnosed with type 2 diabetes (T2D) or cardiovascular disease (CVD).

2. Methods

Study data was collected in a population survey, the Harmonica (Harjavalta Risk Monitoring for Cardiovascular Disease) project, which was carried out in south-western Finland in the rural towns of Harjavalta and Kokemäki in 2005–2007. An invitation to participate in the project, a validated type 2 diabetes risk assessment form (The Finnish Diabetes Risk Score questionnaire (FINDRISC) [11], available at <https://www.diabetes.fi/english>), a cardiovascular risk factor survey and a measuring tape for waist circumference measurement were mailed to all residential inhabitants between the ages of 45–70 years (n = 6013). FINDRISC-score ≥ 12 indicates that estimated 1 in 6 and ≥ 15.1 in 3 will develop T2D within 10 years [11]. Participants were asked to complete and return the risk factor survey to the healthcare centre if they were willing to participate in the project. Participation and all the tests included were free of charge. The participation rate was 74% (4450/6013).

In the risk factor survey, the participants were asked to report the latest measure of their blood pressure, their use of antihypertensive medication, any history of gestational diabetes or hypertension, self-measured waist circumference at the level of the umbilicus, and family history (parents/siblings) of coronary heart disease, myocardial infarction or stroke. A FINDRISC score ≥ 12 in Harjavalta or, for logistics reasons ≥ 15 in Kokemäki was also regarded as a risk factor. Of the 4450 respondents, 3072 (69.0%) had at least one risk factor but no manifested CVD or diabetes. They were invited to further examination performed by a trained study nurse. Valid data of OGTT was available in 2659 study persons.

Blood samples were obtained after at least 12 h of overnight fasting and PG levels and lipid profiles were determined. The OGTT was performed by ingestion of a glucose load of

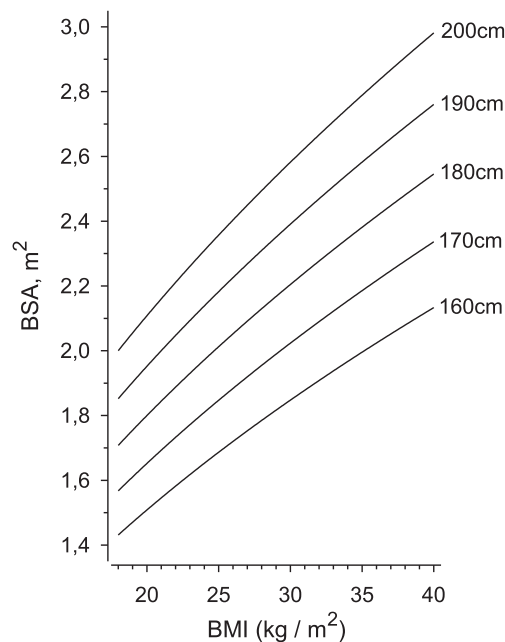


Fig. 1 – Relationship between height, body mass index (BMI) and body surface area (BSA).

75 g of anhydrous glucose dissolved in water. PG was measured before and 2-h after from capillary whole blood using the HemoCue Glucose 201+ system (Ängelholm, Sweden). The results were converted from capillary whole blood to capillary PG values by the analyzer. The WHO 1999 criteria [12] were used to classify glucose disorders. On the basis of 2hPG alone, the participants were classified into categories of newly diagnosed type 2 diabetes (T2D), impaired glucose tolerance (IGT) and normal glucose tolerance if their 2hPG were ≥ 12.2 , $8.9\text{--}12.1$, and < 8.9 mmol/l, respectively. On the basis of FPG alone, participants were classified into categories of newly diagnosed T2D, impaired fasting glucose (IFG) and normal fasting glucose, using the thresholds of ≥ 7.0 , $6.1\text{--}6.9$ and ≤ 6.0 mmol/l, respectively. We combined IGT and IFG as intermediate hyperglycemia (IH). The ratio of 2hPG and FPG was used to illustrate the magnitude of the 75 g glucose dose to elevate PG level in relation to fasting conditions in persons with different body sizes. Plasma total cholesterol, triglycerides and HDL cholesterol were measured enzymatically (Olympus AU604). LDL cholesterol was calculated by Friedewald's formula.

Blood pressure was measured by a study nurse using a calibrated mercury sphygmomanometer. The participants were at least 5 min in a sitting position, and the mean of two readings taken at intervals of at least 2 min was used. Weight, height and waist circumference were measured by a study nurse. BMI was calculated as weight (kg) divided by the square of height (m^2). Waist circumference was measured at the level midway between the iliac crest and the lowest rib margin. BSA was calculated according to the Mosteller formula $[\text{weight (kg)} \times \text{height (cm)} / 3600]^{1/2}$ [13]. Study subjects were divided into five BSA levels: I $< 1.70 \text{ m}^2$, II $1.70\text{--}1.87 \text{ m}^2$, III $1.88\text{--}2.02 \text{ m}^2$, IV $2.03\text{--}2.22 \text{ m}^2$, V $> 2.22 \text{ m}^2$, corresponding 12.5, 25, 25, 25, and 12.5% of the total distribution.

Education years, leisure-time physical activity (LTPA), smoking status and Alcohol Use Disorders Identification Test (AUDIT) [14] were assessed at the clinic after the participants completed self-administrated questionnaires. LTPA was classified as high if the LTPA was ≥ 30 min at a time and performed six or more times a week, as moderate if LTPA ≥ 30 min at a time four to five times a week, otherwise the LTPA was classified as low.

2.1. Ethical approval

The ethics committee of Satakunta hospital district reviewed and approved the study protocol and consent forms. All participants provided written informed consent for the project and subsequent medical research.

2.2. Statistical analysis

The descriptive statistics are presented as means with SDs or as counts with percentages. Statistical significances for the unadjusted hypothesis of linearity across categories of BSA were evaluated by using the Cochran-Armitage test for trend, logistic models, and an analysis of variance with an appropriate contrast. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type test was used. The relationship between diabetes and BSA was modelled using restricted cubic splines (with 4 knots, placed according to Harrell's recommended percentiles) logistic regression model. Regression analyses were used to identify the relative effects of height and weight as predictors of FPG and 2hPG using standardized regression coefficients Beta (β). The Beta value is a measure of how strongly each predictor variable influences the criterion (dependent) variable. The beta is measured in units of standard deviation. Correlation coefficients were calculated by the Pearson method. The normality of the variables was tested by using the Shapiro-Wilk W test. A Stata 15.1 (Stata-Corp LP; College Station, Texas, USA) statistical package was used for the analysis.

3. Results

The study included 2659 participants at increased cardiovascular risk with a mean age of 58 ± 7 years, 56% were women. Table 1 shows the characteristics of the participants according to five BSA level groups. The two lowest BSA categories were dominated by women, the two highest by men. Participants with higher BSA were more likely to be younger, to have higher systolic and diastolic blood pressure, higher plasma glucose and triglyceride levels, and lower HDL cholesterol and total cholesterol levels. BSA was positively associated with other anthropometric measures, AUDIT score, use of statins and antihypertensive medication, but inversely with LTPA.

The prevalence of impairment in glucose regulation increased linearly with rising BSA levels. In subjects with normal glucose tolerance, FPG was positively and the 2hPG/FPG ratio negatively associated with BSA. In patients with new onset T2D, the 2hPG/FPG ratio was inversely related to BSA (Table 2).

Table 1 – The clinical and anthropometric characteristics of the participants according to body surface area levels.

	I <1.70 m ² N = 332	II 1.70–1.87 m ² N = 674	III 1.88–2.02 m ² N = 668	IV 2.03–2.22 m ² N = 662	V >2.22 m ² N = 323	P for linearity
BSA, m ² , mean (SD)	1.63	1.79	1.95	2.11	2.35	..
Women, n (%)	318 (96)	571 (85)	339 (51)	172 (26)	75 (23)	<0.001
Age, mean (SD)	59 (7)	59 (7)	58 (7)	58 (7)	57 (7)	<0.001
Education years, mean (SD)	10.6 (2.8)	10.5 (2.7)	10.3 (2.7)	10.3 (2.7)	10.3 (2.6)	0.12
Height, cm, mean (SD)	159 (5)	164 (6)	169 (7)	175 (8)	179 (9)	<0.001
Weight, kg, mean (SD)	60 (5)	71 (4)	81 (4)	92 (6)	112 (12)	<0.001
BMI, kg/m ² , mean (SD)	23.9 (2.6)	26.6 (2.8)	28.7 (3.7)	30.5 (4.2)	35.5 (5.9)	<0.001
WC, cm, mean (SD)	79 (7)	88 (7)	96 (7)	103 (8)	116 (11)	<0.001
FPG, mmol/l	5.38 (1.26)	5.41 (0.77)	5.59 (1.04)	5.75 (1.14)	6.13 (1.68)	<0.001
2hPG, mmol/l	7.39 (2.19)	7.23 (1.88)	7.34 (2.17)	7.44 (2.45)	7.99 (2.81)	<0.001
TC, mmol/l, mean (SD)	5.50 (0.96)	5.47 (0.97)	5.41 (0.95)	5.30 (0.98)	5.25 (1.03)	<0.001
HDL-C, mmol/l, mean (SD)	1.82 (0.46)	1.71 (0.44)	1.53 (0.41)	1.41 (0.39)	1.27 (0.33)	<0.001
LDL-C, mmol/l, mean (SD)	3.20 (0.83)	3.21 (0.89)	3.28 (0.87)	3.25 (0.90)	3.25 (0.94)	0.29
Triglycerides, mmol/l, mean (SD)	1.13 (0.64)	1.25 (0.64)	1.36 (0.67)	1.52 (0.83)	1.76 (0.85)	<0.001
Blood Pressure, mmHg, mean (SD)						
Systolic	139 (19)	139 (19)	140 (18)	142 (18)	144 (20)	<0.001
Diastolic	81 (10)	82 (9)	84 (10)	86 (10)	89 (11)	<0.001
Current smoker, n (%)	60 (18)	109 (16)	112 (17)	121 (18)	61 (19)	0.47
AUDIT score, mean (SD)	3.1 (4.0)	3.6 (4.1)	4.7 (4.8)	5.7 (5.2)	6.2 (5.5)	<0.001
LTPA, n (%)						<0.001
Low	41 (13)	72 (11)	110 (17)	140 (22)	105 (34)	
Moderate	140 (43)	341 (52)	339 (52)	324 (51)	150 (48)	
High	144 (44)	243 (37)	199 (31)	177 (28)	57 (18)	
Current medication, n (%)						
Statins	31 (9)	65 (10)	84 (13)	109 (16)	46 (14)	<0.001
Antihypertensives	69 (21)	178 (26)	211 (32)	277 (42)	168 (52)	<0.001

Abbreviations: BSA, body surface area; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AUDIT, Alcohol Use Disorders Identification Test; LTPA, leisure-time physical activity.

Table 2 – Prevalence of glucose tolerance categories and plasma glucose levels according to body surface area levels.

	I N = 332	II N = 674	III N = 668	IV N = 662	V N = 323	P for linearity
Glucose tolerance						<0.001
NGT, n (%)	281 (85)	554 (82)	532 (80)	487 (74)	201 (62)	
IH, n (%)	29 (9)	92 (14)	91 (14)	106 (16)	62 (19)	
T2D, n (%)	22 (7)	28 (4)	45 (7)	69 (10)	60 (19)	
NGT, mean (SD)						
FPG, mmol/l	5.11 (0.51)	5.18 (0.49)	5.25 (0.46)	5.32 (0.48)	5.31 (0.41)	<0.001
2hPG, mmol/l	6.94 (1.49)	6.91 (1.43)	6.92 (1.63)	6.86 (1.70)	7.02 (1.91)	0.95
2hPG/FPG ratio	1.37 (0.30)	1.34 (0.29)	1.32 (0.32)	1.30 (0.33)	1.33 (0.36)	0.018
IH, mean (SD)						
FPG	6.23 (0.52)	6.29 (0.44)	6.37 (0.36)	6.34 (0.25)	6.34 (0.39)	0.21
2hPG	8.36 (1.85)	7.95 (1.87)	8.07 (1.97)	7.61 (1.88)	8.16 (1.93)	0.43
2hPG/FPG ratio	1.35 (0.33)	1.27 (0.33)	1.28 (0.33)	1.20 (0.30)	1.29 (0.32)	0.21
T2D, mean (SD)						
FPG	7.68 (3.71)	7.08 (1.66)	7.97 (2.22)	7.87 (2.10)	8.51 (2.48)	0.076
2hPG	13.08 (3.63)	12.70 (2.80)	12.71 (3.35)	12.41 (3.47)	12.45 (3.26)	0.48
2hPG/FPG ratio	2.11 (0.74)	2.05 (0.59)	1.84 (0.57)	1.75 (0.53)	1.66 (0.45)	<0.001

Abbreviations: NGT, normal glucose tolerance; IH, intermediate hyperglycemia (defined as IFG or IGT); T2D, type 2 diabetes; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose.

When adjusted for age, sex, waist circumference, alcohol intake, current smoking, and LTPA, the BSA level showed an inverse linear relationship with the 2hPG and 2hPG/FPG ratio

in all categories of glucose tolerance (p for linearity < 0.001). Among persons with normal glucose tolerance, the 2hPG/FPG ratio decreased from 1.47 (95% CI: 1.42–1.52) to 1.23

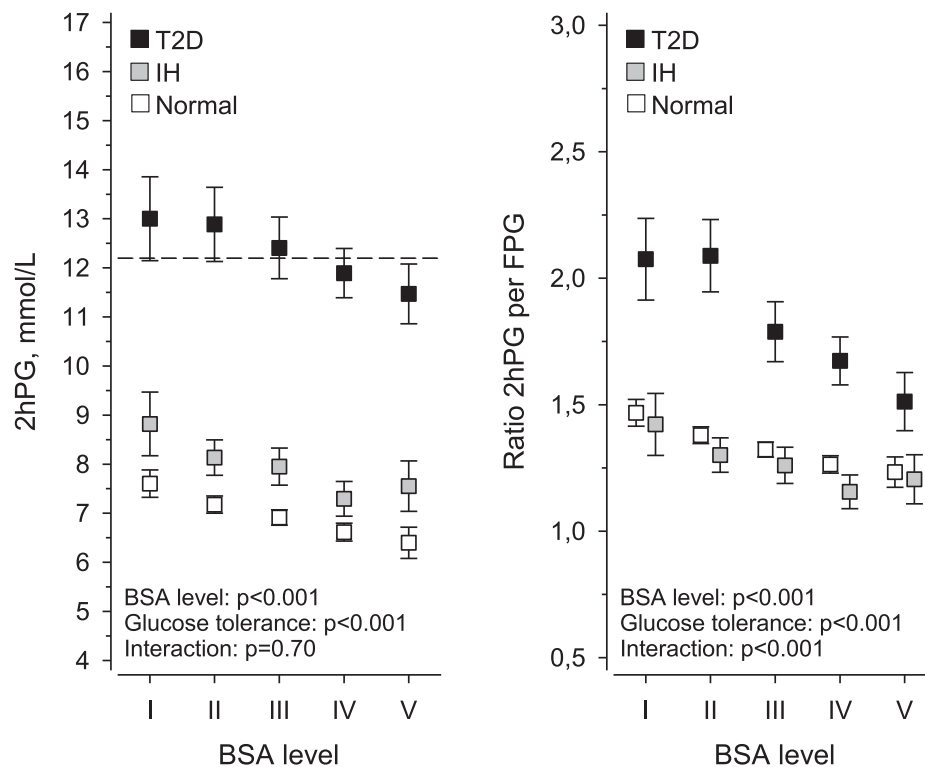


Fig. 2 – Mean 2-hour plasma glucose (2hPG) and 2hPG per fasting plasma glucose (FPG) ratio. By body surface area and glucose tolerance category. Adjusted for age, smoking status, leisure time physical activity, alcohol intake, waist circumference and gender. Error bars are for 95% confidence intervals. The dashed line indicates the 2hPG diagnostic cut-off value for type 2 diabetes.

(95% CI: 1.17–1.29) across the rising BSA levels. The corresponding figures among subjects with newly diagnosed T2D were 2.08 (95% CI: 1.91–2.24) and 1.51 (95% CI: 1.40–1.62). There was an interaction between the BSA and 2hPG/FPG ratio ($p < 0.001$) but not between BSA and 2hPG ($p = 0.70$) (Fig. 2).

Fig. 3 shows the adjusted proportion of new T2D diagnoses based on the OGTT. BSA was inversely related with new T2D diagnoses (p -value for linearity < 0.001). In univariate regression analysis, both height and weight showed a positive relationship with FPG, the effect of weight being more pronounced. The relationship of weight was positive with 2hPG, whereas height showed an inverse association with 2hPG (Fig. 4).

4. Discussion

This study indicates that the smaller the adjusted BSA of a population, the higher the proportion of new T2D cases diagnosed by 2hPG in an OGTT will be. Thus, there is a possibility that the diagnosis of T2D made by an OGTT is a false positive result in a relatively small individual, and a false negative result in a relatively larger individual. This might be a major importance in certain ethnic groups characterized by small BSA. It is well known that the diagnostic tests, i.e. fasting glucose, OGTT, and glycated haemoglobin (HbA_{1c}), do not detect diabetes or impairment in glucose regulation in the same individual [15,16]. This may be partially the consequence of different body sizes affecting 2hPG in an OGTT.

In the present study, increasing levels of BSA were associated with higher levels of several cardiometabolic risk factors. However, when adjusted for age, sex, smoking status, leisure time physical activity, alcohol intake, and waist circumference, higher BSA level was inversely associated with 2hPG and 2hPG/FPG ratio in all categories of glucose tolerance. This suggests that BSA, when the effect of central adiposity is removed, partly determines the rate of glucose metabolism. We used 2hPG/FPG ratio to examine to what degree the 75 g glucose dose increased PG concentration in relation to fasting glucose concentrations. Independently of glucose tolerance category, 2hPG was lower in relation to FPG when BSA was larger. This seems to indicate that the uniform 75 g glucose dose has smaller impact on 2hPG level when body size is larger even if FPG concentration has been taken into account. Moreover, as a consequence of their smaller body size, women may be more often diagnosed with T2D or impaired glucose tolerance than men.

We used 2hPG/FPG ratio to examine to which degree the 75 g glucose dose elevated PG level in relation to fasting conditions. Independently of glucose tolerance category, 2hPG was lower in relation to FPG when BSA was larger. This seems to indicate that the uniform 75 g glucose has smaller impact on 2hPG level when body size is larger even if FPG concentration has been taken into account. Moreover, as a consequence of their smaller body size, women may be more often diagnosed with T2D or impaired glucose tolerance than men.

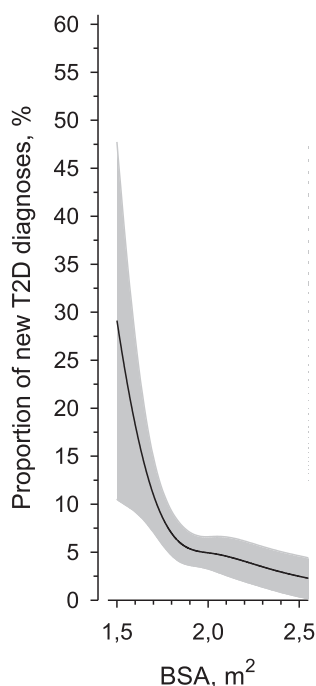


Fig. 3 – Proportion of newly diagnosed type 2 diabetes (T2D) based on 2hPG values according to body surface area (BSA). The curves were derived from a 4-knot restricted cubic splines logistic regression models. The models were adjusted for age, sex, smoking status, leisure time physical activity, alcohol intake, and waist circumference. The grey area represents a 95% confidence interval.

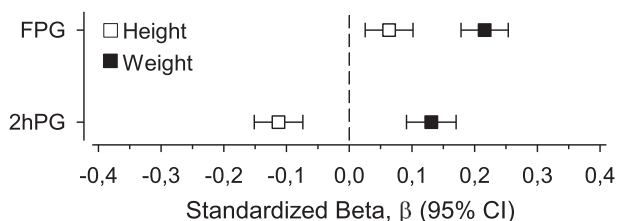


Fig. 4 – Univariate relationships between body size predictive variables (height and weight) and diagnostic variables (FPG and 2hPG). The standardized beta coefficients (β) with 95% confidence intervals.

Adjusted BSA may be regarded as the framework of the human body in which the organs responsible for glucose absorption, utilisation and production function. It is reasonable to assume that the larger the framework, the larger the internal organs and skeletal muscle mass. Indeed, a larger BSA has been shown to predict higher total liver volume [17] and higher infrarenal aortic diameter [18]. Moreover, gut glucose half-life shows an inverse relationship with body height and fat-free mass [19,20]. Recently, left ventricular size and mass was reported to be proportional to height and even more to BSA in US professional basketball players [21].

The basal metabolic rate is seldom considered in studies focusing upon glucose tolerance and glucose metabolism. It has been estimated that under fasting conditions, glucose uptake by the brain is 0.43 mmol/min, by skeletal muscle

0.12 mmol/min, and by the heart 0.08 mmol/min per 1.73 m² BSA [22]. This basal energy consumption of the human body may partly explain our findings that even among subjects with normal glucose tolerance, adjusted 2hPG level and 2hPG/FPG ratio decreased with increasing body size. This probably reflects the physiological response of organs in a larger body to the same 75 g glucose load which is also given to smaller persons. Stančáková et al. demonstrated that peripheral insulin sensitivity is already decreased within the normal range of FPG and 2hPG both in non-obese and obese individuals [23]. This finding may be explained by differences in the body sizes of the study subjects.

Although we propose that 2hPG values may be biased by body size, it is noteworthy that 2hPG predicted all-cause mortality better than elevated fasting glucose in a meta-analysis performed by Huang et al. [24] In eleven studies included in the meta-analysis focusing upon individuals with impaired glucose regulation, body height or BSA were not adjusted. Our results suggest that higher 2 h glucose concentration during 75 g OGTT identifies individuals with on average smaller body size. Importantly, it is well known that short adult stature is a risk factor for cardiovascular and all-cause mortality [25–27]. Thus, it is possible that after controlling for height-related confounders, such as body height or BSA, 2hPG values might not be associated with increased risk of mortality.

The major limitation of our study is the cross-sectional setting. Therefore, it is not possible to define causal relationships between body size and its inverse effect on 2hPG concentrations. However, the study participants represent a typical primary care population in which an OGTT is frequently used as a screening tool to detect defects in glucose regulation. It is well known that the reproducibility of an OGTT is rather poor in asymptomatic individuals. Assigning the study participants into five groups of BSA makes our results comparable to other populations based on the fact that BSA is normally distributed in the general population. However, results may not be directly generalizable to populations with different ethnic background. Further, part of the data was gathered by self-evaluation forms in which compliance and correct responses are not possible to verify.

In conclusion, body size has a considerable impact on the result of a standardized OGTT. Smaller individuals are more likely to be diagnosed as glucose intolerant than relatively larger sized individuals, despite the elevated metabolic risk seen in larger individuals. Given that OGTT is a time and effort consuming test both for patients and laboratory personnel, the medical community might abandon OGTTs and use FPG and/or HbA_{1c} as diagnostic tests for glucose disorders. The alternatives, adjusting the glucose dose to the height or BSA of a person as recommended fifty years ago [1] or using different cut-off values for 2hPG for individuals with different body sizes, are too cumbersome for clinical practice.

5. Contributors

SP wrote the first draft and participated writing and editing of the report. SR participated in drafting of the report. KH designed the study and did statistical analysis. JGE participated writing and editing the report and oversaw the prepara-

tion of the report as senior author. PEK designed the study, collected data, participated in the statistical analysis, drafting and preparation of the report and oversaw the preparation of the report as senior author.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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